IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ron L. HALE et al.	
Application No.:	10/719,540	Examiner: J. H. Alstrum-Acevedo
Filed:	November 20, 2003	Group Art Unit: 1616
For:	METHOD FOR TREATING HEADACHE WITH LOXAPINE (AS AMENDED)	Confirmation No.: 3439

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Commissioner for Patents
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a notice of appeal. The review is requested for the reasons stated below.

A final Office Action was mailed in the above-captioned application on February 1, 2010. Claims 1, 5-9 and 12-24 are pending in the application. Claims 1, 5-9 and 12-24 stand rejected.

I. Claim Rejections – 35 U.S.C. § 103

A. Claims 1, 5-9, 12-15 and 24

Claims 1, 5-9 and 12-24 are pending in the present application. Claims 1, 5-9, 12-15 and 24 stand rejected as obvious under 35 U.S.C. § 103 over Burns, et al., (U.S. Patent No. 5,284,133, "Burns") in view of Drug Information Handbook, 2nd edition (Lexi-Comp, Inc.: Cleveland, 1994-1995, pp 554-555, "DIH") .

Claim 1 as pending states in its entirety:

> *A method for treating headache comprising administering to a subject in need of* ***headache*** *relief, an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine, and prodrugs of loxapine wherein* ***0.3 to 6.0 mg*** *of loxapine is administered, or an amount of a salt or prodrug of loxapine is administered that produces in the subject a blood concentration of loxapine equivalent to the administration of 0.3 to about 6.0 mg of loxapine. (emphasis added)*

Applicant respectfully submits that the teachings relied upon by the Examiner fail to state a prima facie case of obviousness pursuant to 35 U.S.C. §103(a). Among other things, the prior art references must teach or suggest all claim limitations if a prima facie obviousness case is to be made. The claim element which most clearly distinguishes the invention of claim 1 from the prior art is the treatment of headache with loxapine. Prior to Applicant's disclosure, the use of loxapine for the treatment of headache was unknown.

The Examiner cites Burns as teaching loxapine hydrochloride as a headache analgesic. The cited passage reads,

> For example, with neuroleptics, psychotropics, narcotic antagonists, other central nervous system (CNS) drugs and headache analgesics, such as proclorperazine, fluphenazine hydrochloride, chlorpromazine, trifluperazine hydrochloride, thioridazine hydrochloride, loxapine hydrochloride, and haloperidol decanoate, anxiolytics such as alprazolam, busiprone and diazepam; antidepressants such as amitriptyline, clomipramine, doxepine and fluoxetine; antisomnatics such as flurazepam, temazepam and trizolam; anticonvulsants such as carbemazepine, phenytoin and clorazepam; antinausea drugs such as meclizine, …
> Burns et al. Column 7, lines 12-23. (emphasis added)

The passage lists a variety of drug classes ("neuroleptics, psychotropics, narcotic antagonists, other central nervous system (CNS) drugs and headache analgesics") and then lists variety of drugs ("such as proclorperazine, fluphenazine hydrochloride, chlorpromazine, trifluperazine hydrochloride, thioridazine hydrochloride, loxapine hydrochloride, and haloperidol decanoate") as part of a long sentence concerning drugs for which there may be a tendency of some patients to overdose themselves. Burns et al., col. 7, lines 12-28.

The Drug Information Handbook, 2nd edition, cited by the Examiner, refers to loxapine's "onset of neuroleptic effect" (Drug Information Handbook, at 555;). The class of "neuroleptics" is the first drug class listed in the passage cited by the Examiner that includes loxapine

hydrochloride. Thus, the Burn's passage does not disclose loxapine as a headache analgesic, it merely lists loxapine in its known role as an example of a neuroleptic, as noted in the DIH. The Burns reference is directed to an inhalation device –it has nothing to do with the treatment of headache or the administration of loxapine. It is noteworthy that the only place in the reference that loxapine is cited is in the one, poorly written sentence cited by the Examiner. To conclude that loxapine is disclosed as a headache analgesic, under these circumstances, when no other reference can be found teaching loxapine is a headache analgesic must be the result of hindsight reasoning based on knowledge gleaned only from the Applicant's disclosure. Under McLaughlin, (443 F.2d 1392, 1395) this is improper.

Claims 5 and 9 further require that the headache is a "migraine headache." Significantly, later in the same sentence cited by the Examiner, the list of drugs in the class of "migraine headache analgesics" does not include loxapine hydrochloride. (Burns at col. 7, lines 25-27). Thus, even the Examiner's strained reading of Burns et al. would require that loxapine hydrochloride is not a drug for the treatment of migraine headache. Thus, for at least this additional reason, claims 5 and 9 are not obvious over Burns et al. because Burns et al. teaches away from using loxapine hydrochloride for the treatment of migraine headache.

An internet search of the terms "loxapine" and "headache" illicit either Applicants' patent/application portfolio or headache as a possible side effect of loxapine when used as a neuroleptic. (Google search performed on January 24, 2009). The presently claimed invention has thus far been patented in Europe, Australia, and Mexico, all three of which have performed searches, and have not found any references, besides the Applicant's patent family, wherein loxapine is used in the treatment of headaches.

Claim 1 is further limited by a dosage element of "*…wherein **0.3 to 6.0 mg** of loxapine is administered…*". With regard to dosage, the Drug Information Handbook outlines the usual dose range to be 60-100 mg/day for oral administration (first pass metabolism) or 12.5-50 mg every 4-6 hours IM (bypassing first pass metabolism) of loxapine for use in treatment as a neuroleptic drug. The Examiner argues that the dosing range would have been apparent to a skilled artisan that the dosages required for inhalation administration would be lower than those for oral administration (DIH), because via inhalation administration the disadvantage of first-pass metabolism of the administered drug by the liver and kidneys is avoided. However, the IM dosage range listed above is still well above the claimed dose. Further, the AHFS Drug

Information Premier Drug Information Database for the American Society of Health-system Pharmacists (see Appendix; also found at http://www.ashp.org/mngrphs/essentials/a382311e.htm ; or http://www.medscape.com/druginfo/monograph?cid=med&drugid=14375&drugname=Loxapine+Succinate+Oral&monotype=monograph&secid=3) states, "systemic bioavailability of the parent drug after oral administration of loxapine reportedly was approximately one-third that found after IM administration of an equivalent dose, which may be related to first pass metabolism." Given the above discussed pharmacokinetics, the limitation of 0.3 to 6.0mg of loxapine in the claims is well below the dose disclosed in the Drug Information Handbook, even considering the effects of first pass metabolism. Further, the dosage from the Drug Information Handbook refers to the dosage used for a neuroleptic affect. Nothing in the prior art teaches a range of 0.3 to 6.0mg of loxapine for the treatment of headache, as loxapine was not known for its use as a headache analgesic. Moreover, the DIH indicates that an initial dose of 10 mg be administered twice daily and that the dosage be increased until psychotic symptoms are controlled. It is not clear how one of skill in the art would take this instruction of "increase dosage until psychotic symptoms are controlled" as a starting point to arrive at a dose that is effective in treating headaches. These dosages taught by Drug Information Handbook to treat psychotic symptoms would not convey to one of skill in the art what dosages are appropriate to treat headache. Moreover, Applicant teaches at paragraphs [0024]-[0025] how the dosage of loxapine to treat migraine headache differs from the dosage of loxapine for treatment of schizophrenia. See specification at paragraphs [0024]-[0025]. Thus the claim element of "*...wherein **0.3 to 6.0 mg** of loxapine is administered...*" is not taught or suggested by the prior art.

Thus, the prior art does not teach or suggest each and every element of Claim 1 or Claim 24. As Claims 5-9 and 12-20 depend from Claim 1, the prior art does not teach or suggest each and every element of Claims 5-9 and 12-20. Thus, the Examiner has failed to establish even a *prima facie* case of obviousness as each and every element of claims 1, 5-9, 12-20 and 24 is not taught or disclosed by Burns et al. in view of DIH.

With regard to the outstanding obviousness-type double patenting rejections, Applicant has agreed to file the appropriate terminal disclaimers once the scope of the claims has been determined.

For the foregoing reasons, the application is believed to be in a condition for allowance. Applicant respectfully requests that the Examiner's rejections be withdrawn and a Notice of Allowance be issued by the review panel.

Respectfully submitted,

Date: April 30, 2010

/Katherine Lobel-Rice/

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